Biochimica et Biophysica Acta 1837 (2014) e126–e129

Contents lists available at ScienceDirect

Biochimica et Biophysica Acta

journal homepage: www.elsevier.com/locate/bbabio

S12 – Participant organized symposium — Energetics of disease-causing microorganisms and the potential for drug discovery

S12.L1

Targeting bacterial energetics to produce new antimicrobials

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The emergence and spread of drug resistant pathogens and our inability to develop new antimicrobials to combat resistance (phenotypic and genetic) has motivated scientists to consider non-traditional targets where human homologs clearly exist. Cellular bioenergetics is an area showing promise for the development of new antimicrobials, but the success of this area will only emerge by understanding the role of these energetic processes (e.g. respiration and oxidative phosphorylation) under conditions that prevail in host tissues. In this session, we will examine the recent developments in the field suggesting cellular energetics as a target space for the development of new antimicrobials.

doi:10.1016/j.bbabio.2014.05.032

S12.L2

The chemical biology of ATP synthase inhibition in mycobacteria

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Energy metabolism has emerged as a new target-pathway for development of new anti-tubercular drugs [1]. We investigated a selective ATP synthase inhibitor, bedaquiline (TMC207)[2-4] and its target, mycobacterial ATP synthase [5]. In this poster we present insight into the chemical biology of this new drug/target system, elucidating the bacterial metabolic response upon bedaquiline treatment. BDQ treatment of mycobacteria triggered upregulation of pathways involved in ATP production, including enzymes of the glycolytic pathway, the pyruvate dehydrogenase complex and the tricarboxylic acid cycle, as well as ATP synthase and the cytochrome bd oxidase [6]. In contrast, major biosynthetic pathways were downregulated upon BDQ treatment, including ribosomal protein synthesis, DNA biosynthesis and synthesis of mycolic acids, a key component of the mycobacterial cell envelope [6]. These changes in the mycobacterial proteome reflect a general strategy employed by mycobacteria for preserving ATP pools, minimizing consumption of cellular ATP and utilizing alternative ATP-generating pathways. [1] D. Bald, A. Koul. Advances and strategies in discovery of new antibacterials for combating metabolically resting bacteria. Drug Discov. Today 18 (2013) 250-255. [2] K. Andries, P. Verhasselt, J. Guillemont, et al. A diarylquinoline drug active on the ATP synthase of Mycobacterium tuberculosis. Science 307 (2005) 223-227. [3] A. Koul, N. Dendouga, K. Vergauwen et al. Diarylquinolines target subunit c of mycobacterial ATP synthase. Nat. Chem. Biol. 3 (2007) 323-324. [4] A.C. Haagsma, I. Podasca, A. et al. Probing the interaction of the diarylquinoline TMC207 with its target mycobacterial ATP synthase. PLoS One 6 (2011) e23575 [5] A.C. Haagsma, N.N. Driessen, M.M. Hahn et al. ATP synthase in slow- and fast-growing mycobacteria is active in ATP synthesis and blocked in ATP hydrolysis direction. FEMS Microbiol. Lett. 313 (2010) 68-74. [6] A. Koul, L. Vrancks, N. Dhar et al. Delayed bactericidal response of Mycobacterium tuberculosis to bedaquiline involves remodeling of bacterial metabolism. Nat. Commun. 5 (2014) 3369.

doi:10.1016/j.bbabio.2014.05.033

S12.L3

Oxidative phosphorylation — A potential drug target in *Mycobacterium tuberculosis*

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With the increasing occurrence of drug resistance in diseases including tuberculosis (TB) new drug targets, new lead compounds, and new antimicrobial strategies are all of interest. Recently TMC207/Bedaquiline, a compound that inhibits ATP synthesis in mycobacteria, was approved for use in patients with multidrug-resistant or extensively drug resistant-TB suggesting that oxidative phosphorylation is a vulnerable drug target in mycobacteria. This view is supported by studies from our laboratory and others that suggest menaquinone synthesis (required for electron transport in mycobacteria) is also a valid drug target. Recent data indicates that saturation of a single isoprene unit in the menaquinone of *Mycobacterium tuberculosis* represents a novel virulence factor for this pathogen. Rv0561c, annotated as a possible oxidoreductase, in the *Mycobacterium tuberculosis* H37Rv genome and MSMEG1132 in *Mycobacterium smegmatis* are shown to encode enzymes that increase the mass of menaquinone by two AMU. Mass spectral analysis unambiguously demonstrated that these enzymes did not reduce the aromatic ring moieties, but increased the mass of the isoprenyl side chains by reducing one double bond. Thus, this previously undescribed reductase catalyzes the final step in the synthesis of the predominant form of menaquinone found in mycobacteria and, presumably, other Gram-positive bacteria that synthesize partially saturated